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(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 587 790 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
03.01.1996 Bulletin 1996/01

(51) Int. Cl.⁶: A61K 9/72, C09K 3/30

(86) International application number: PCT/US92/04618

(21) Application number: 92913922.8

(87) International publication number: WO 92/22287
(23.12.1992 Gazette 1992/32)

(22) Date of filing: 08.06.1992

(54) NON-CHLOROFLUOROCARBON AEROSOL FORMULATIONS

FLUORCHLORKOHLLENWASSERSTOFFFREIE AEROSOLFORMULIERUNGEN

COMPOSITIONS AEROSOL SANS CHLOROFLUOROCARBONES

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL
PT SE

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(43) Date of publication of application:
23.03.1994 Bulletin 1994/12

(56) References cited:

(60) Divisional application: 95101762.3

EP-A- 0 372 777	WO-A-90/07333
WO-A-90/11754	WO-A-91/04011
WO-A-91/11173	WO-A-91/11495
WO-A-91/14422	WO-A-92/00061
WO-A-92/00062	WO-A-92/00107
WO-A-92/08446	

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Remarks:

Consolidated with 92305253.4/0518601 (European
application No./publication No.) by decision dated
15.06.94.

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Description

INTRODUCTION TO THE INVENTION

5 The present invention is directed at aerosol formulations which are substantially free of chlorofluorocarbons (CFC's). More specifically, the present invention is directed at formulations substantially free of CFC's and having particular utility in medicinal applications, especially in metered dose pressurized inhalators (MDI's).

Metered dose inhalators have proven to be an effective method for delivering medicaments orally and nasally. They have been used extensively for delivering bronchodilating and steroidal compounds to asthmatics and may also be useful
 10 for delivering other compounds such as pentamidine and non-bronchodilator anti-inflammatory drugs. The rapid onset of activity of compounds administered in this manner and the absence of any significant side effects have resulted in a large number of compounds being formulated for administration via this route. Typically, the drug is delivered to the patient by a propellant system generally comprising one or more propellants which have the appropriate vapor pressure and which are suitable for oral or nasal administration. The more preferred propellant systems typically comprise propellant 11, propellant 12, propellant 114 or mixtures thereof. Often the vapor pressure of the propellant systems is
 15 adjusted by admixing a liquid excipient with the propellant.

However, propellants 11, 12 and 114 belong to a class of compounds known as chlorofluorocarbons, which have been linked to the depletion of ozone in the atmosphere. It has been postulated that ozone blocks certain harmful UV rays and that a decrease in the atmospheric ozone content will result in an increase in the incidence of skin cancer. In
 20 the 1970's certain steps were taken to reduce the CFC emissions from aerosols. Other propellants, such as hydrocarbons, were used, or the product was delivered in a different manner. Because CFC usage in medicinal applications is relatively low i.e. less than 1% of total CFC emissions, and because of the health benefits associated with metered dose inhalators, steps were not taken at that time to restrict the use of CFC propellants in metered dose inhalators.

However, continuing and more sophisticated ozone measurements have indicated that the earlier restrictions in
 25 CFC usage were insufficient and that additional, significant steps should be taken to drastically reduce CFC emissions. Recently, recommendations have been made that CFC production be virtually discontinued by the end of this century. As a result, it may not be possible to continue to use CFC propellants in the intermediate and long term. While some efforts have been made to use non-pressurized metered dose inhalators, many of these devices have not been completely successful. Many do not deliver uniform doses, are mechanically complex, do not provide the 100-200 doses per
 30 unit of current aerosol containers, are difficult for individuals to utilize, are bulky and/or cumbersome for the patients to use, particularly when they have an acute need for the medication.

As a result, there is a need for aerosol formulations substantially free of CFC's. Non-CFC propellants must meet several criteria for pressurized metered dose inhalators. They must be non-toxic, stable and non-reactive with the medicament and the other major components in the valve/actuator. One propellant which has been found to be suitable is
 35 $\text{CF}_3\text{-CH}_2\text{F}$, also known as Freon 134a, HFA 134a, HFC 134a or 1,1,1,2 tetrafluoroethane. However, the physical properties, i.e. vapor pressure, polarity, solubility, density and viscosity of HFC 134a differ from those of commonly used propellants. Propellant HFC 134a has a vapor pressure of 5.84×10^5 newton/meter² absolute (84.7 psia), which is too high for use in metered dose inhalators. In addition, commonly used surfactants may be insoluble in HFC 134a. Moreover, where the medicament is to be delivered as a solution, the medicament may not be readily soluble in this propellant.
 40 The density and polarity difference between HFC 134a and the previously used CFC propellant may result in a different delivery of the medicament when HFC 134a replaces a CFC propellant. The medicament may cream, settle or agglomerate in the non-CFC propellant even though this did not occur in the CFC propellant.

The use of HFA 134a previously has been disclosed for use in medicinal inhalators. European Patent Publication No. 0 372 777 is directed at medicinal aerosol formulations incorporating Freon 134a and an adjuvant having a higher
 45 polarity than the propellant. This publication lists several possible adjuvants and surfactants for use in combination with the propellant and the medicament.

International patent application No. WO 91/04011 discloses the combination of 1,1,1,2 tetrafluoroethane and a powdered medicament pre-coated with a non-perfluorinated surfactant prior to dispersing the powdered medicament in the propellant. Pages 6-7 of the publication list suitable surfactants for use with the propellant. A perfluorinated adjuvant
 50 optionally could be added. However, the pre-coating of the medicament may not be advantageous, since it adds an additional, complex step to the manufacturing process.

Research Disclosure No. 30161, May 1989 discloses that non-CFC propellants such as fluorohydrocarbons may be used in pressurized medicaments delivered directly to the lungs e.g. bronchodilators.

U.S. Patent No. 4,174,295 discloses the combination of HFC 134a with various chlorofluorocarbons and optionally
 55 a saturated hydrocarbon.

U.S. Patent No. 2,885,427 discloses the use of HFC-134a as an aerosol propellant.

U.S. Patent No. 3,261,748 discloses the use of HFC-134a for anesthesia.

U.S. Patent Nos. 4,129,603, 4,311,863, 4,851,595 and European Publication No. 379,793 also disclose the use of HFC-134a as an aerosol propellant.

However, the specific combinations noted above may not provide the desired solubility, stability, low toxicity, exact dosage, correct particle size (if suspension) and/or compatibility with commonly used valves assemblies of metered dose inhalers. Further, in all cases it is taught that aerosol formulations containing HFC-134a as propellant require in addition a carrier, surfactant, excipient or other such aerosol component.

SUMMARY OF THE INVENTION

The present invention is directed at non-toxic formulations substantially free of CFC's, having improved stability and compatibility with the medicament and valve components and which are relatively easily manufactured.

The present invention also is directed at formulations which may be utilized in present aerosol filling equipment with only relatively minor modifications and without pre-coating the medicament.

Accordingly, the invention provides an aerosol formulation consisting of:

A. an effective amount of a medicament; and

B. 1,1,1,2-tetrafluoroethane; and

C. optionally, one or more components selected from one or more of the following:

preservative;

buffers;

antioxidants;

sweeteners; and

taste masking agents.

In an embodiment of the invention, the medicament is selected from albuterol; mometasone furoate; beclomethasone dipropionate; isoproterenol; heparin; terbutaline; rimeterol; pirbuterol; disodium cromoglycate; isoprenaline; adrenaline; pentamidine; ipratropium bromide; and salts and clathrates thereof. It is preferred that the medicament is selected from albuterol; albuterol sulfate; beclomethasone dipropionate; beclomethasone dipropionate clathrates; and mometasone furoate.

In another aspect of the invention, the aerosol formulation as defined above is for treatment of asthma, in which instance the medicament is selected from albuterol, mometasone furoate, beclomethasone dipropionate and salts and clathrates thereof.

The medicaments of the present invention may include any pharmaceutically active compounds which are to be delivered by oral inhalation or nasally. Typical classes of compounds include bronchodilators, anti-inflammatory compounds, antihistamines, antiallergics, analgesics, antitussives, anti-anginal medications, steroids, corticosteroids, vasoconstrictors and antibiotics. Specific compounds within these classes of compounds are albuterol, mometasone furoate, beclomethasone dipropionate isoproterenol, heparin, terbutaline, rimeterol, pirbuterol, disodium cromoglycate, isoprenaline, adrenaline, pentamidine and ipratropium bromide. These compounds may be utilized either as the free base, as a salt, or as a clathrate depending upon the stability and solubility of the active compound in the specific formulation. Where clathrates are utilized, P-11 and hexane clathrates are particularly preferred.

Where the active compound forms a suspension, the particle size should be relatively uniform, with substantially all the particles preferably ranging between about 0.1-25 microns, preferably 0.5-10 microns, more preferably 1-5 microns. Particles larger than 25 microns may be held up in the oropharyngeal cavity, while particles smaller than about 0.5 micron preferably are not utilized, since they would be more likely to be exhaled and, therefore, not reach the lungs of the patient.

The formulations of the present invention may be filled into the aerosol containers using conventional filling equipment. Since propellant 134a may not be compatible with all elastomeric compounds currently utilized in present aerosol valve assemblies, it may be necessary to substitute other materials, such as white buna rubber which mitigate the adverse effects of propellant 134a on the valve components. One may optionally use an actuator device with a spacer to reduce force of the spray from an MDI.

To assure uniform dispersion of the active ingredient, the formulations typically will include the following components:

	Range(wt%)	Preferred Range(wt%)	Most Preferred Range(wt%)
Medicament	0.01-1	0.03-0.7	0.05-0.5
Propellant	99-99.99	99.3-99.97	99.5-99.95

Depending on the particular application, the container may be charged with a predetermined quantity of formulation for single or multiple dosing. Typically, the container is sized for multiple-dosing, and, therefore, it is very important that

the formulation delivered is substantially uniform for each dosing. For example, where the formulation is for bronchodilation, the container typically is charged with a sufficient quantity of the formulation for 200 charges.

Suitable suspensions may be screened in part by observing several physical properties of the formulation, i.e. the rate of particle agglomeration, the size of the agglomerates and the rate of particulate creaming/settling and comparing these to an acceptable standard. Suitable solutions may be screened by observing the solubility of the medicament over the entire recommended storage temperature range.

Suspension of the present invention preferably may be prepared by either the pressure filling or cold filling procedures well-known in the art.

For metered dose inhalators, suspensions may be particularly preferred for efficacy and stability considerations.

Those skilled in the art may choose to add one or more preservative, buffer, antioxidant, sweetener and/or flavors or other taste masking agents depending upon the characteristics of the formulation.

Examples below further describe representative formulations of the present invention.

Example 1	
Component	wt%
Mometasone Furoate	0.1
HFC-134a	99.9

Example 2	
Component	wt%
Beclomethasone Dipropionate P-11 Clathrate	0.1
HFC-134a	99.9

While the examples above have been directed at mometasone furoate and beclomethasone dipropionate clathrates, it is contemplated that other orally or nasally administered medicaments could be utilized.

Claims

1. An aerosol formulation consisting of:

A. an effective amount of a medicament; and

B. 1,1,1,2-tetrafluoroethane; and

C. optionally, one or more components selected from one or more of the following:

preservatives;

buffers;

antioxidants;

sweeteners; and

taste masking agents.

2. A formulation according to claim 1 wherein the medicament is selected from albuterol; mometasone furoate; beclomethasone dipropionate; isoproterenol; heparin; terbutaline; rimeterol; pirbuterol; disodium cromoglycate; isoprenaline; adrenaline; pentamidine; ipratropium bromide; and salts and clathrates thereof.

3. A formulation according to claim 2 wherein the medicament is selected from albuterol; albuterol sulfate; beclomethasone dipropionate; beclomethasone dipropionate clathrates; and mometasone furoate.

4. A formulation according to any preceding claim containing 0.01 to 1 percent by weight medicament.

5. A formulation according to claim 4 containing 0.03 to 0.7 percent by weight medicament.

6. A formulation according to claim 5 containing 0.05 to 0.5 percent by weight medicament.
7. A formulation according to any preceding claim wherein the medicament is a powder having a mean particle size of 1 to 5 microns.

Patentansprüche

1. Aerosol-Formulierung, bestehend aus:

A. einer wirksamen Menge eines Medikamentes und

B. 1,1,1,2-Tetrafluorethan und

C. gegebenenfalls einer oder mehreren Komponenten, ausgewählt aus einem oder mehrerer der Folgenden:

Konservierungsmittel;

Puffer;

Oxidationsschutzmittel;

Süßstoffe und

geschmacksmaskierende Mittel.

2. Formulierung nach Anspruch 1, wobei das Medikament aus Albuterol; Mometasonfuroat; Bedomethasondipropionat; Isoproterenol; Heparin; Terbutalin; Rimiterol; Pirbuterol; Dinatriumcromoglycat; Isoprenalin; Adrenalin; Pentamidin; Ipratropiumbromid und Salzen und Clathraten davon ausgewählt ist.

3. Formulierung nach Anspruch 2, wobei das Medikament aus Albuterol; Albuterolsulfat; Bedomethasondipropionat; Beclomethasondipropionat-Clathraten und Mometasonfuroat ausgewählt ist.

4. Formulierung nach einem der vorhergehenden Ansprüche, die 0,01 bis 1 Gew.-% Medikament enthält.

5. Formulierung nach Anspruch 4, die 0,03 bis 0,7 Gew.-% Medikament enthält.

6. Formulierung nach Anspruch 5, die 0,05 bis 0,5 Gew.-% Medikament enthält.

7. Formulierung nach einem der vorhergehenden Ansprüche, wobei das Medikament ein Pulver mit einer mittleren Teilchengröße von 1 bis 5 Mikrometer ist.

Revendications

1. Formule en aérosol consistant en :

A. une quantité efficace d'un médicament; et

B. du 1,1,1,2-tétrafluoroéthane; et

C. facultativement, un ou plusieurs composants sélectionnés parmi un ou plusieurs de ceux qui suivent :

conservateurs;

tampons;

antioxydants;

édulcorants; et

agents masquant le goût.

2. Formule selon la revendication 1 où le médicament est sélectionné parmi l'albutérol, le furoate de mométasone; le dipropionate de bédométhasone; l'isoprotérénol; l'héparine; la terbutaline; le rimiterol; le pirbutérol; le cromoglycate disodique; l'isoprénaline; l'adrénalin ; la pentamidine; le bromure d'ipratropium; et leurs sels et clathrates.

3. Formule selon la revendication 2 où le médicament est sélectionné parmi l'albutérol, le sulfate d'albutérol; le dipropionate de bédométhasone; les clathrates de dipropionate de bédométhasone; et le furoate de mométasone.

4. Formule selon toute revendication précédente contenant 0,01 à 1 pour cent en poids du médicament.

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5. Formule selon la revendication 4 contenant 0,03 à 0,7 pour cent en poids du médicament.
6. Formule selon la revendication 5 contenant 0,05 à 0,5 pour cent en poids du médicament.
- 5 7. Formule selon toute revendication précédente où le médicament est une poudre ayant une dimension de particules de 1 à 5 micromètres.

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